The History of MS Research Points the Way to the Future

Substantial progress has been made in developing MS therapeutics. However, successfully treating MS continues to present great challenges. Treatment choices are still made largely by trial and error, leading to less than ideal outcomes for many people with the disease. Here at ACP, we got to wondering how and why we arrived at this place, where there exists a multitude of drugs and a deficit of knowledge about how they work in each patient. We decided to review the history of MS research to see if it held answers to this question.

More than 2.3 million people worldwide have multiple sclerosis (MS), an autoimmune disease that interrupts the circuitry between the brain and the body and usually strikes young adults. In people with MS, the body’s immune system attacks its own myelin and produces focal lesions (plaques) within the brain and spinal cord. Myelin is a substance that insulates nerves and enables them to quickly send and receive essential messages throughout the body. If this description sounds simple and straightforward, don’t be fooled. It is a very complex disease that has challenged—and in some cases has stumped—researchers for 150 years.

Several distinct events are required to initiate the MS disease process and these are still not fully understood. Among the factors considered to play a role are genetics and one or more environmental triggers, such as a virus, a nutritional factor, or smoking. Not all MS patients are alike. The disease presents with four distinguishable subtypes: relapsing remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and relapsing progressive (RPMS). MS is not only different in each person, it can change over time within an individual. For example, relapsing disease can become progressive disease. Symptomatic differences also occur, depending on the location and number of lesions. Even more problematically, there are no consistent biomarkers for the disease. Some scientists actually believe that rather than one disease, MS consists of several, closely related demyelinating diseases.

At the moment, there are 13 different drug therapies that have been approved for MS, most for relapsing forms of the illness. Most of these drugs reduce the likelihood of future relapses and hence slow down new damage to the brain and spinal cord. None of the treatments offers a cure, and none are able to reverse the brain and nerve damage that has already occurred. Especially frustrating is the fact that neurologists can’t predict which patients will benefit from a particular drug.
How did we achieve this level of understanding and discover multiple disease modifying therapies? Not surprisingly, the story of MS research reflects the history of medicine, which has moved from the simple observation and classification of diseases in the 18th and 19th centuries, to the probing of complex biologic systems and the application of sophisticated technologies and techniques in the 20th and 21st centuries. It is a story of brilliance as well as serendipity.

**Discovery in the 19 Century**

Once scientists had begun to analyze illnesses scientifically, MS was one of the first they identified. By 1868, a French scientist conducting an autopsy on an MS patient discovered plaques in the brain and connected the location of the plaque with the MS symptoms the patient had suffered when alive. Then myelin was discovered in 1878, opening the way for scientists to understand the connection between myelin degeneration and MS.

**1900 – 1950**

In the early 20th century, chemical dyes were discovered and made it possible to view nerve cells under a microscope for the first time, and MS researchers clearly saw damaged myelin in nerve cells in the brain. By 1928, they had discovered oligodendrocytes, the cells that make myelin. Around the same time, nerve transmissions were successfully recorded for the first time and soon thereafter, the role of myelin in efficiently transmitting nerve signals to the rest of the body was understood.

This left scientists hunting for the cause of demyelination. In the early part of the 20th century, knowledge of bacteria and viruses grew as researchers developed techniques for studying them in the laboratory. It had been observed that people vaccinated against viral illnesses sometimes developed symptoms resembling MS and this, in turn, precipitated exploration of the possible role played by viruses (and immunizations against viruses) in triggering demyelination. Just before the outbreak of World War II, researchers at Rockefeller University demonstrated on animals that immune cells could also produce MS-like symptoms. This same animal model would later prove useful in a broader understanding of autoimmunity, the process by which the body attacks its own immune system and the hallmark of several diseases.

The fact that MS attacks people when they are still young has always made the hunt for treatments and a cure compelling. But one could say that the public campaign to find a cure for MS was launched in 1946, with the founding of the National MS Society. The first research grant the Society awarded was to study the immunology of MS, and from that point forward, patients and their loved ones were organized and actively engaged with the hunt for diagnoses, causes, treatments and a cure.
1950 – 1970
The post-war economic boom of the 1950’s drove an explosion of scientific research in America. A wave of government spending was spawned by two influences: a comprehensive new federal science and technology policy and the anti-Communist sentiment that dollars spent for science were dollars spent for democracy. The ascendancy of the Cold War, as much as anything else, precipitated the 1950 formation of the National Science Foundation—a major funnel for government funding of basic research, primarily for the university sector. The new foundation had a Division of Biological and Medical Sciences, although its mission was limited to supporting basic research so that it wouldn’t compete with the more clinically oriented research of the National Institutes of Health. Throughout the 1950s, Congress regularly added $8 million to $15 million to the NIH budget each year. By 1956, its budget had risen to almost $100 million. By the end of the decade, it was supporting some 10,000 research projects at 200 universities and medical schools at a cost of $250 million.

Perhaps the most meaningful medical story of the time was that of Jonas Salk’s “conquest of polio.” A Salk biographer described the response to the April 12, 1955, vaccine announcement: “More than a scientific achievement, the vaccine was a folk victory, an occasion for pride and jubilation…. People observed moments of silence, rang bells, honked horns.” 1 The discovery raised the public’s expectations of scientists’ ability to cure serious diseases. Moreover, it underscored the value of public advocacy and engagement in the hunt for treatments and cures. Throughout the ’40’s and early ’50’s the National Foundation for Infantile Paralysis (one of the first successful research-advocacy organizations) collected millions of ten-cent donations from the general public to fund polio research through its “March of Dimes.”

While scientific advances in chemistry and other fields allowed for significant progress in drug discovery and production, the DNA era dawned. Watson and Crick determined the structure of the genetic material in 1953. The way in which genes control biologic functions, including the immune system, became clearer from subsequent research. Scientists isolated and studied the immune system cells, including B-cells and T-cells, in their search for ways to halt MS. In the 1960’s, clinicians developed standard guidelines for MS diagnoses, and scales to rate the levels of disability and the parts of the nervous system affected by the disease. These tools categorized people with MS and paved the way for enrolling them in clinical trials.

1970 – 2000
Coincident with the boom in high technology, the 1970’s and 1980’s saw the invention of Computed Axial Tomography (CAT) scans and Magnetic Resonance Imaging (MRI) scans, both of which dramatically improved the visualization of the brain and spinal cord, enabling MS lesions to be quantified in living patients. The technique helped to measure the severity of the disease and could thus be used to evaluate the effect of drugs on disease progression. It also resulted in faster diagnoses of the disease. In 1970, the average time from a person’s first symptom of MS until a definite diagnosis was 7 years. The use of MRI reduced the average time to 6 months. The hunt for treatments picked up speed and began to produce results. Steroids, which suppress immune activity, were found to reduce the severity of MS attacks. In addition, the discovery that myelin fragments in the bloodstream seemed to
prevent MS-like disease in animals led to the creation of copolymer I (Copaxone).

The advent of biotechnology allowed for the discovery and development of protein based drugs that affected major processes such as cellular signaling within the human body. These new drugs resulted in new treatments for a broad range of diseases. According to one account, biotechnology was born during a meeting at a Hawaiian delicatessen in 1972. A Stanford University medical professor and a biochemist from the University of California, San Francisco, had studied plasmids, the ringlets of DNA contained in bacteria, and discovered that they could propagate and clone the plasmids in the bacteria. In addition, they had worked with a revolutionary enzyme called EcoRI that could cleave the double-stranded DNA molecule to produce single-stranded ends with identical termini. Their late night chat in the deli led to a scientific achievement that later rocked the world of science. Within a year, they had cloned DNA molecules made by splicing together DNA fragments of two different plasmids, thus creating recombinant DNA and the ability to efficiently produce recombinant versions of biologically active signaling molecules.

In the following years, dozens of biotech firms were launched. The industry began with a focus on human proteins made in bacteria and on antibodies. It then moved on to immunological treatments for cancer and other diseases. In the 1980’s and 1990’s came a wave of neurobiology companies, followed by a wave of genomics companies.

A neurologist at the State University of New York, Buffalo wondered whether interferon, named for its ability to interfere with viral proliferation and being produced at Buffalo’s Roswell Park Cancer Center, might help people with neurological diseases because it was thought that viral infection might be a cause of some of them. From a host of neurological diseases, he decided to study its impact on MS, although he later acknowledged the serendipity of this decision. "We first considered Lou Gehrig's disease, but ultimately we decided on MS, because Buffalo happens to be in a geographic region where MS occurs with high frequency and there were so many patients in Western New York with MS. It was just luck." This work spurred the development of interferon beta by a number of biotech firms. Today, interferon beta is still instrumental in reducing MS relapses.

2000 – the Present
Greater understanding of MS expanded the possible targets of drug therapies for MS at a time when the biopharmaceutical industry was burgeoning. While the new biological drugs were game changers, they were also complex and costly to manufacture. The first drugs launched demonstrated that there was pent-up demand for MS treatments, while the size of MS drug sales, combined with the chronic nature of the disease made them profitable. This then encouraged other companies to develop MS treatments. By 2000, multiple
pharmaceutical companies had MS drugs in development. The tools of molecular genetics next allowed for the discovery of molecules that reside on the surface of immune cells. These molecules regulate the activity of the adaptive immune response that plays an important role in the pathology of MS. Recombinant versions of humanized monoclonal antibodies (MAbs) have been central to the treatment of diseases such as cancer. Two immune cell-directed MAbs, natalizumab and alemtuzumab, have now been approved for the treatment of MS.

Meanwhile, the mapping of the human genome focused attention on the genetic causes of many diseases. The work on genetics, along with an increase in computational capabilities, spurred the growth of bioinformatics and systems biology, and led to the creation of vast information sets that have come to be known as “Big Data.” Multiple studies comparing tens of thousands of MS and control subjects, along with other studies on pairs of twins raised in different parts of the world, have demonstrated that, while there is no single “MS gene,” the genetics of the human immune system does play a significant role in determining who contracts the disease.

Big data makes it possible for medical researchers to take a macroscopic view of health, including the ability to recognize patterns or clues to disease genesis and development. It is precisely this understanding that led in 2001 to the formation of Accelerated Cure Project and the creation of the ACP Repository, which distributes bio-samples for research, collects data and remains at the core of what we do.

Does this brief history of MS research explain why we now have multiple therapies, some of which attack the disease in different ways, but all of which defy our ability to predict their effectiveness in any given patient? Undoubtedly, it demonstrates the sheer complexity of the disease. MS involves two highly inscrutable human systems: (1) the immune system with its myriad of cells and signaling factors and receptors that interact in ways we yet barely understand, and (2) the central nervous system which we can’t biopsy at will like we can other tissues, so understanding how it works in health or disease requires using suboptimal techniques such as autopsy, animal models and imaging (although imaging gets better all the time, offering hope for the future).

The history of MS research does reveal the extent to which our knowledge of the disease is shaped by our observation of its reaction to interventions. Seen in that light, the availability of multiple therapies has assisted in our understanding of the disease. This suggests that the next research frontier is to observe and better understand how, and when each therapy works. Read on to learn about an exciting ACP initiative aimed at doing just that.

2 New York Times, November 10, 2001; Obituary of Dr. Lawrence Jacobs.